ISSN 2515-8260 Volume 09, Issue 07, 2022

LEPTOMENINGEAL METASTASIS IN CARCINOMA BREAST MOLECULAR SUBTYPES – A RETROSPECTIVE ANALYSIS

1) Dr Pankaj Gupta
Chief Surgical Pathologist Blupath Lab Ujjain, MP
drpankaj9@gmail.com
2) Dr Prerna Walecha
Consultant pathologist and histopathologist at Nipun Path Lab, Rudrapur, Udham Singh Nagar (Uttarakhand)
Pin 263153
3) Dr. Mimansha
Patel, Professor, Department of Oral Pathology and Microbiology, Triveni Dental College, Bodri, Bilaspur, Chhattisgarh
Email - mimanshapatel_24@yahoo.com
4) Dr. Kanchan Shrivastava
SRL Ujjain Consultant Pathology
kanchan2315@gmail.com
5) Dr Sanjay Deb
Senior Consultant Pathology and Lab Director, Dr Remedies Labs, New Delhi
sanjaydeb@hotmail.com
6) Dr Ruchika Solanki
BPT MPT Consultant Physiotherapist Birla Hospital
Ujjain, MP ruchikasolanki231@gmail.com

ABSTRACT

Background: Leptomeningeal metastasis (LM) is a condition that develops when malignant cells from an extrameningeal primary tumor invade the leptomeninges. Patients with solid tumors (5-8%) and patients with lymphohematopoietic neoplasms (5-15%) are both diagnosed with it. Among solid tumors, leptomeningeal metastases are most frequently caused by metastases to the breast and lungs. The management of the patient depends on the early detection of LM. Cerebrospinal fluid (CSF) cytological analysis is still essential for LM diagnosis. The molecular subtypes of breast cancer should affect LM propensity because they are correlated with tumor behavior and prognosis.

Methodology: Records of patients who underwent CSF examination and had meningeal involvement with clinical symptoms were kept for seven years at an oncology facility in North India. The data was analyzed for CSF involvement in the tumor subtypes after the cases were divided into molecular subtypes by hormone receptor profiling, HER2, and the proliferation index of the breast tumors.

Results: Of the 1332 patients at our hospital who were diagnosed with breast cancer during the study period, 41 patients (3%) had CNS symptoms, and 22 patients (53% of them) had LM confirmed by CSF cytology. The majority of these (40.9%) belonged to the molecular subtype of

triple-negative breast cancer, which was followed by HER2 (36.36%), Luminal A (13.63%), and Luminal B (9.09%).

Conclusion: The results show that triple-negative breast cancer is more likely than other subtypes to metastasize to the CNS, which is consistent with its more aggressive behavior. As a result, complications like leptomeningeal metastasis may be predicted by the molecular subtyping of breast carcinoma.

Key words: Leptomeningeal metastasis, Breast Carcinoma, Molecular subtypes

INTRODUCTION

Leptomeningeal metastasis (LM), also referred to as neoplastic meningitis, is a condition caused by metastatic infiltration of the leptomeninges by malignant cells from extrameningeal primary tumors. Leptomeningeal metastasis is diagnosed in 5 to 8 percent of patients with solid tumors and in 5 to 15% of patients with lymphohematopoietic neoplasms (1). Metastases from the breast and lungs are the most common causes of leptomeningeal metastasis among solid tumors (1). Newer drugs and aggressive chemotherapy regimens have resulted in increased survival of patients with malignancies, resulting in an increased incidence of late-onset metastasis and thus making LM a common clinical problem. (1-3). Early detection of LM is imperative for patient management. Cytological examination of cerebrospinal fluid (CSF) remains pivotal in the diagnosis of LM.

Breast cancer is a heterogeneous disease showing marked clinical and morphological diversity. This has resulted in the development of a molecular classification of breast carcinoma based on gene expression profiling detected by tumor cell receptor expression. The molecular subtypes correlate with tumor behavior and prognosis and therefore should also influence the propensity for LM. We thought that it would be worth studying which molecular subtypes tend to metastasize to the meninges.

AIMS AND OBJECTIVE

Aim of study is correlation of molecular subtypes of breast cancer classified by hormone profiling by Immunohistochemistry with the leptomeningeal metastasis proven by CSF cytology.

MATERIAL AND METHODS

Archived cases of carcinoma breast undergoing CSF examination for suspected meningeal involvement were studied. The data was retrieved from Department of Pathology of a Oncology Centre of North India from year 2007 to 2014. The tumor grade, stage and tumor Oncotype based on hormone profiling results were compared with meningeal involvement. Molecular subtypes were classified as

- Luminal A - ER+ and /or PR +, HER2 –ve
- Luminal B - ER+ and /or PR+, HER2 +
- HER 2 type - ER-ve, PR-ve, HER2 +
- Triple Negative breast cancer (TNBC) - ER, PR and HER 2 Negative.

Descriptive statistics were used to determine patient’s demographic and clinicopathological characteristics. Hypothesis test were conducted at alpha = 0.05 level, with 95% confidence limit.

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In order to compare different tumor features in the four molecular subtypes of patients, chi-square test was used. For those in which Chi-square test was inappropriate because of small sample size, ANOVA and linear regression analysis were done. Following factors were analyzed

- Age at LM(≤50 and >50)
- Modified Blood Richardson histological grade (I, II and III),
- TNM stage (I, II, III, IV) at the time of diagnosis.

RESULTS

1332 patients at our facility had breast cancer diagnosed during the study period. 3 of the 41 patients had CNS symptoms, and 22 (53%) of them had LM confirmed by CSF cytology. The molecular subtype Triple Negative (TNBC) accounted for the majority of these, with 9 cases (40.90%), followed by HER-2 with 8 cases (36.36%), Luminal A with 3 cases (13.63%), and Luminal B with 2 cases (9.09%).

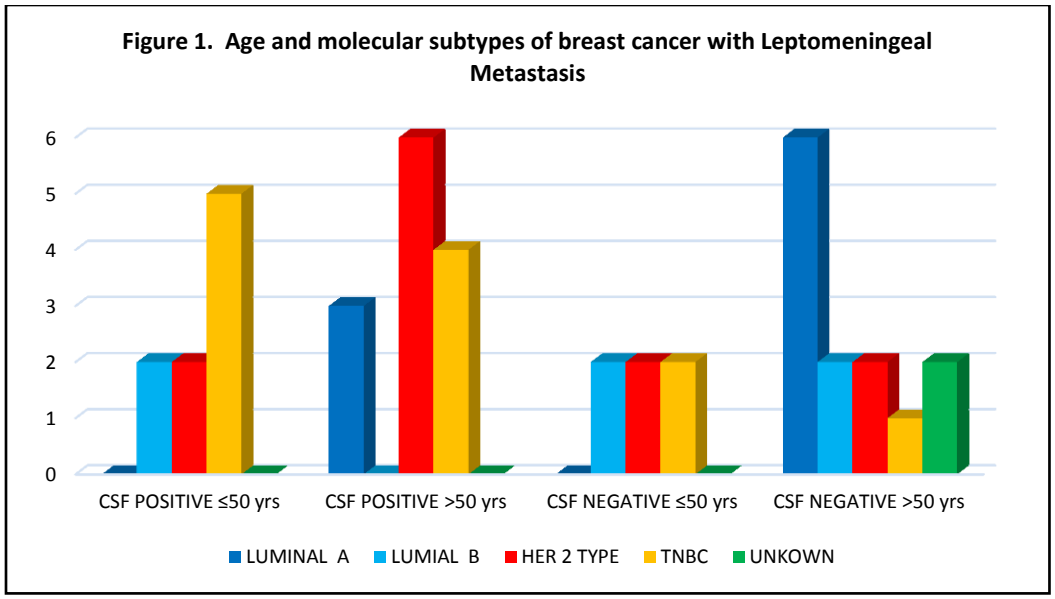
There were 9 patients under the age of 50 and 13 patients over the age of 50 when the clinical profile of CSF-positive cases was examined. These 9 patients were made up of 5 TNBC (55.55%), 2 HER2 type (22.22%), 2 Luminal B (22.22%), and no Luminal A subtype patients. Four patients had TNBC (30.76%), three had Luminal A (23.77%), and six patients over the age of 50 had HER2 (46.15%). As a result, TNBC made up the majority of the patients in the premenopausal age group, while HER2 made up the majority of the patients in the postmenopausal age group. With a p value of 0.155, this data demonstrated that triple-negative breast cancer is more common in younger age groups and is more likely to be LM than any other molecular subtype. **(Table 1)**

MOLECULAR SUBTYPES	CSF POSITIVE (22)		CSF NEGATIVE (19)		TOTAL (41)
	≤50 yrs	>50 yrs	≤50 yrs	>50 yrs	
LUMINAL A	0	3	0	6	9
LUMIAL B	2	0	2	2	6
HER 2 TYPE	2	6	2	2	12
TNBC	5	4	2	1	12
UNKOWN	0		0	2	2
Chi square test value	6.602		6.658		
P value	0.085*		0.155*		

Table1. Age and molecular subtypes of breast cancer with Leptomeningeal Metastasis

*No statistically significant association exists (p>0.05)

ISSN 2515-8260 Volume 09, Issue 07, 2022



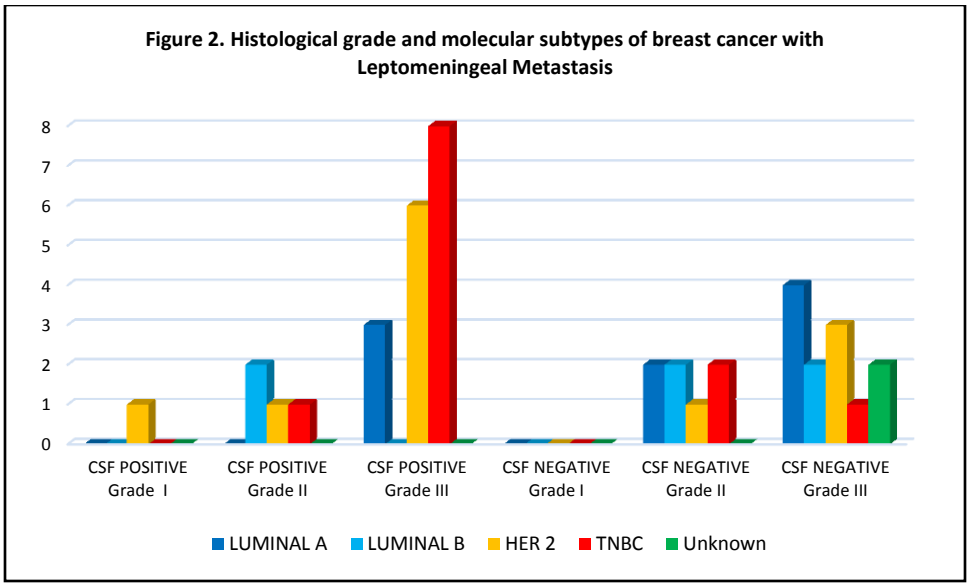
The majority of the CNS symptomatic patients in our study had tumors of histological grade III (27 of 41, or 65.85%), and of these, 17 (62.96%) tested positive for LM. Eight (47.07%) of the 17 patients had TNBC, six (35.29%) had HER2 types, three (17.64%) had Luminal A subtypes, and none had Luminal B subtypes. 11 patients (11 of 41, or 26.82%) had histological grade II tumors, of which 4 cases (36.36%) had LM positive tumors, two of which were Luminal B (50%), and one each of TNBC and HER2 type (25%). Only one grade I case (2.43%) with a HER2 molecular subtype was found in our data, and it was linked to LM. These findings with a p value of 0.577, demonstrate that while molecular subtypes are crucial for predicting tumor behavior even though higher tumor grades are linked to a higher risk of LM. Regardless of histologic grade, patients with more aggressive molecular subtypes like TNBC and HER2 were positive for LM. **(Table 2)**

Table 2. Histological grade and molecular subtypes of breast cancer with Leptomeningeal Metastasis

MOLECULAR SUBTYPES	CSF POSITIVE			CSF NEGATIVE			TOTAL (41)
	Grade I	Grade II	Grade III	Grade I	Grade II	Grade III	
LUMINAL A	0	0	3	0	2	4	9
LUMINAL B	0	2	0	0	2	2	6
HER 2	1	1	6	0	1	3	12
TNBC	0	1	8	0	2	1	12
Unknown	0	0	0	0	0	2	2
Chi square test value	11.957			2.883			
P value	0.062*			0.577*			

*No statistically significant association exists (p>0.05)

ISSN 2515-8260 Volume 09, Issue 07, 2022



Clinical stage at the time of diagnosis is an important prognostic parameter. When this was correlated with molecular subtypes for propensity of LM, it was observed that less aggressive subtypes like Luminal A had no LM at clinical stage IV, where as more aggressive subtypes like TNBC and HER2 type showed CSF involvement even with lower clinical i.e. stage II and III. **(Table 3)**

Table 3. Clinical stage and molecular subtypes of breast carcinoma with Leptomeningeal Metastasis

MOLECULAR SUBTYPES	CSF POSITIVE				CSF NEGATIVE				TOTAL
	Stage I	Stage II	Stage III	Stage IV	Stage I	Stage II	Stage III	Stage IV	
LUMINAL A	0	0	1	2	0	3	1	2	9
LUMINAL B	0	0	2	0	0	1	0	2	5
HER 2	0	1	4	1	0	0	0	4	10
TNBC	0	0	4	4	0	0	0	3	11
Initial clinical stage of 6 cases unkown									
Chi square test value	5.757				7.090				
P value	0.450*				0.312*				

*No statistically significant association exists (p>0.05)

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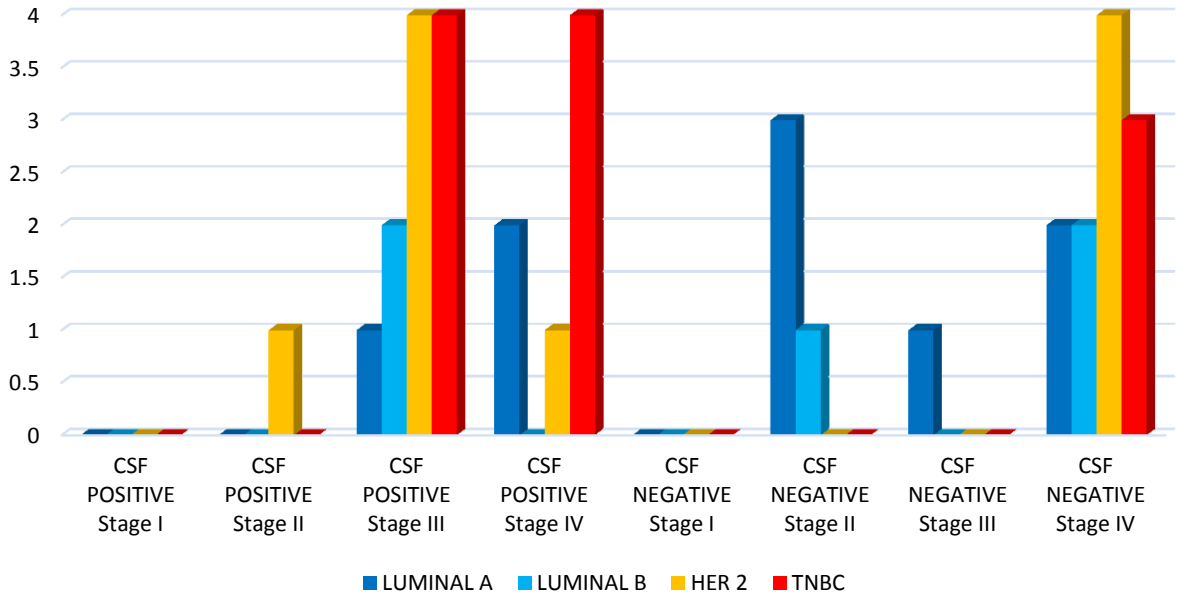
Figure 3. Clinical stage and molecular subtypes of breast carcinoma with Leptomeningeal Metastasis



DISCUSSION

Leptomeningeal metastasis is a late-stage cancer phenomenon in breast cancer. Malignant cells can metastasize to the meninges either by the hematogenous route, which is more common in hematological malignancies, or by the lymphatic route, which is mostly adopted by breast cancer and other solid tumors. Breast cancer patients' survival and therapy have improved, resulting in an increase in the incidence of LM.

According to the National Comprehensive Cancer Network (NCCN) guidelines (4), any one of the following diagnostic criteria is sufficient to diagnose LM, i.e.,

- CSF is positive for tumor cells (positive CSF cytology) (Figs. 1 and 2).
- Radiologic findings in the CNS consistent with LM are independent of supportive clinical findings.
- Clinical signs and symptoms consistent with LM and a non-specific but abnormal CSF analysis (high WBC count, low glucose, and elevated protein) in a patient known to have cancer

With the onset of molecular profiling of breast cancer on the basis of gene expression profiling (5, 6), breast carcinoma can be divided into four basic molecular subtypes: luminal A (ER +ve, PR +ve, HER2 –ve), luminal B (ER +ve, PR +ve, HER2 +ve), HER2 type (ER-ve, PR-ve, HER2 +ve), and triple negative (ER, PR, HER2 negative). This classification is done routinely on the basis of the immunohistochemical expression of these receptors.

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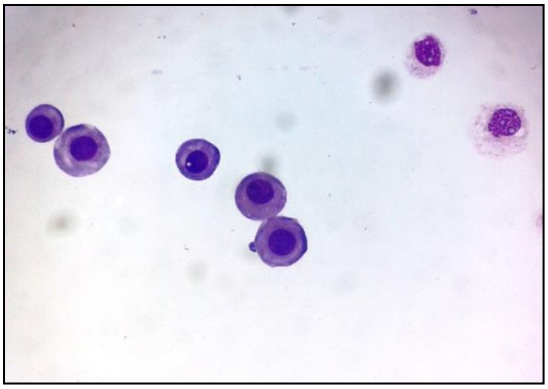

FIGURE 1. METASTATIC INFILTRATING DUCTS CARCINOMA CELLS IN CSF (60X, MGG).

In the present study, molecular subtypes were derived for cases that proved positive for LM by CSF cytology using immunohistochemistry. The molecular subtypes were compared with the age, histological grade, and stage of the patients. All the cases in our study were histologically infiltrating duct carcinomas (no specific type). Among the cases that were positive for LM, the most common molecular subtype was triple negative (40.90%), followed by HER2 type, Luminal A, and Luminal B. The study done by Niwinska A. et al. (7) on 118 breast cancer patients with LM had similar observations with triple-negative breast cancer as the most common subtype.

The most common CNS symptom among these (n = 41) was headache in 46.43% of patients, followed by vomiting (31.0%); others presenting complaints were status epilepticus (12.0%), altered sensorium (14.63%), and para- or hemiparesis. In various studies (1, 2, 7), headache was found to be the most common symptom of patients presenting with leptomeningeal metastasis.

In our study, most of the premenopausal patients (50 years of age) were triple-negative breast cancer and had a higher propensity for LM as compared to postmenopausal patients (>50 years of age), in whom the HER2 subtype was the most common subtype to metastasize. This is in concordance with a previous study done by De la Monte et al. (8), which showed that ER- and PR-negative tumors have a greater propensity to metastasize at a younger age as compared to ER- and PR-positive tumors. Tsukada Y et al. (9) have shown that the median age of patients with CNS metastasis in breast cancer is 5 years younger than the age of patients without CNS metastasis.

ISSN 2515-8260 Volume 09, Issue 07, 2022

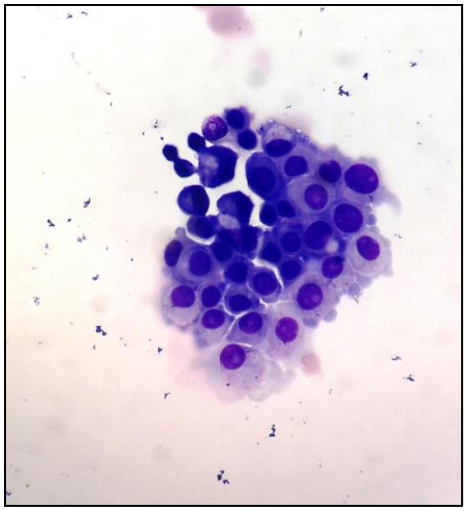

FIG.2 METASTATIC INFILTRATING DUCT CARCINOMA CELLS IN CSF (60X, MGG).

The study demonstrates that although histological grade is a significant single prognostic factor for breast cancer, the molecular subtypes behave irrespective of their histological grade, and more aggressive subtypes like HER2 and TNBC can even present with LM with a lower histological grade.

Once LM is diagnosed in carcinoma of the breast, intrathecal methotrexate is used for the management of these patients. In our study, 8 patients responded well to chemotherapy, and 14 patients died due to LM and associated complications. One patient had metachronous bilateral breast cancer, with the right side diagnosed in 2003 and the left in 2008; she presented with LM in 2009, has responded well to treatment, and is on follow-up.

In our center, among the patients with LM, 14 patients presented within a period of a few months to a year with CNS symptoms after being diagnosed with breast cancer, and the rest within a range of 2 to 4 years. When compared to other molecular subtypes, HER2 type and triple-negative breast cancer had a shorter disease-free survival time.

CONCLUSION

Molecular profiling of breast cancer can be done cost-effectively with immunohistochemistry and is better at predicting the behavior of breast cancer as compared to any other available prognostic parameter. Molecular subtyping of breast cancer at the time of diagnosis is important to predict complications like leptomeningeal metastases, predict the prognosis, and improve survival. Although the findings of our study couldn’t produce any statistically significant findings due to small sample size, the results are significant from the clinical perspective. We recommend further research on larger samples to explore various other clinical aspects.

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