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Bone marrow study of 128 bronchogenic carcinoma patients in a tertiary care hospital

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Abstract: *Background and Aim of study:* Bronchogenic carcinoma has emerged as the most common form of malignant disease globally. Plenty treatment options are available, yet survival rate is substantially low. The stage of disease is an important prognostic parameter and guiding factor for therapeutic decisions & treatment related mortality. The aim of our study was to detect metastatic deposit in marrow, detect correlation of hematological picture with bonemarrow involvement and assess degree of marrow fibrosis. *Materials and Methods:* This was a prospective study comprising of 128 diagnosed patients of bronchogenic carcinoma devoid of known metastatic spread. Patients were subjected to clinic-radiological assesement and biochemical parameters. The patients were subjected to bonemarrow aspiration & trephine biopsy for histopathology. *Main findings:* Bonemarrow metastatic deposits were found in 12 cases (9.37%) in both bone marrow trephine biopsy and aspirate. Aspiration was unable to detect metastasis in 2 cases (likely due to extensive myelofibrosis) where trephine biopsy was useful. Hematological and biochemical parameters showed statistically significant difference in LDH (p= 0.0011) and uric acid level (p=0.0001) in metastatis positive and negative group. *Conclusion reached:* We emphasized that cytological and histological examination of bonemarrow be considered as useful and safe pre-treatment staging procedures in bronchogenic carcinoma because early detection of sites of metastatic spread provides prognostic information.

Keywords: Bronchogenic Carcinoma, Bone Marrow Biopsy, Hematological Correlation.

Introduction

Bronchogenic carcinoma is the largest contributor to cancer related morbidity and mortality globally with 12.4% of total new cancer related deaths being attributed to it [1]. Plenty of treatment options are available for management and plenty are still to come, yet the survival rate is very poor. The stage or extent of disease is an important prognostic parameter and a guiding factor for optimal therapeutic decisions & treatment related mortality [2].

Once the disease has been diagnosed to have metastatic spread to other sites, the management options get very much limited i.e. mainly palliative where treatment with a curative intent cannot be considered. Bone marrow is one of the most common organs involved by the tumors that metastasize by blood stream [3]. Several studies have reported shorter median survival in patients who had bone-marrow metastasis than patients with extensive stage disease without marrow involvement [4]. The presence of two or more micrometastatic cells in the bone marrow of patients with negative nodes (PN0) was a strong predictor of recurrence and had a statistically significant impact on disease-free and overall survival [4]. Bone-marrow infiltration may be suspected on bone pain, pathological fractures, radiological lytic or sclerotic lesions, hypercalcaemia or raised serum alkaline phosphatase and unexplained hematological abnormalities [5].

Henceforth we have tried to assess whether bone marrow examination can be considered as an integral part of initial staging procedure in patients of bronchogenic carcinoma (paricularly non-small cell variety) and whether we can correlate hematological markers with marrow involvement so that

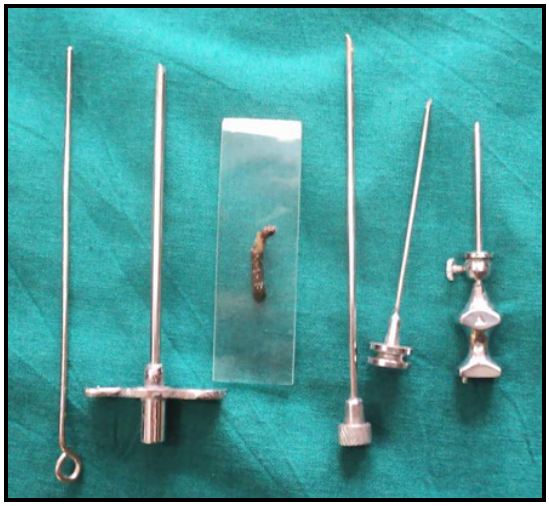
they may be recommended as a surrogate marker for early detection of marrow involvement particularly in Indian perspective where immunohistochemistry studies are not easily available.

Material and Methods

After approval from the institutional ethical committee, total 128 patients of bronchogenic carcinoma diagnosed by FNAC or core biopsy of lung mass or by bronchoscopy guided biopsy were considered for study and evaluation, subject to their willingness and valid consent to undergo this study. Patients already having metastatic spread to other site (metastatic lymph node deposit, positive pleural fluid cytology, hepatic, adrenal or cerebral metastasis), poor general condition, bleeding disorders and local infections were excluded from the study.

All patients were subjected to thorough clinical examination, radiological assesement including chest radiography and CT scan, complete hemogram including platelet count, blood biochemical parameters like sugar, urea, creatinine, liver function test, LDH level, uric acid and calcium levels. Then the patients were subjected to bone marrow aspiration for cytology & trephine biopsy for histopathology along with study of imprint from posterior iliac crest under local anesthesia (Figure 1).

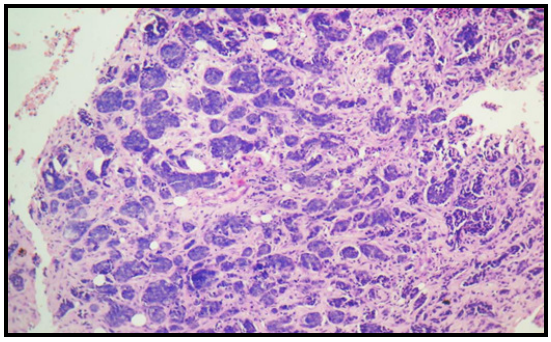
Fig-1: Bone Marrow Biopsy Needle with stellate, Bone marrow Aspiration Needle with Stellate and the Biopsy material procured after the procedure put on a glass slide for Imprint preparation



Bone marrow aspirate was examined by Leishman-Giemsa staining, bone marrow biopsy was examined by routine hematoxylin and eosin staining of decalcified section (formic acid decalcification) [6] and reticulin staining was done by silver impregnation technique done by Gordon & Sweet method [7].

Positive outcome was defined as demonstrable islands / aggregates of epithelial cells, entrapped within desmoplastic stroma on routine histopathology (serial step-cuts of bone marrow biopsy) or any demonstrable aggregates of non-hemopoietic cells in bone marrow aspirated material (Figure 2,3).

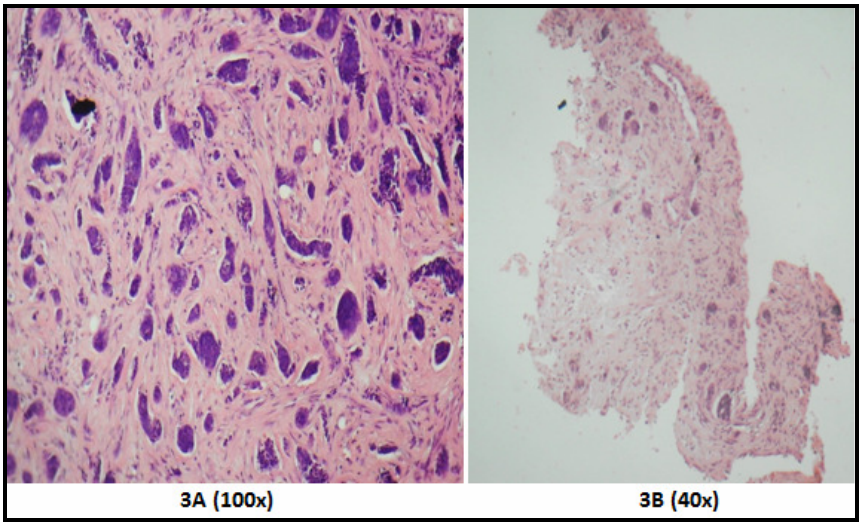
Fig-2: Extensive metastatic deposit of Adenocarcinoma from lung in Bone marrow biopsy (H & E X 100).



Bone marrow was also studied for several other parameters like cellularity, erythropoiesis, myelopoiesis, megakaryopoiesis,

Myeloid: Erythroid Ratio and abnormal non-hemopoietic cells (as an evidence of metastatic deposit). All the collected data were compiled and analyzed by appropriate statistical methods later on using multiple logistic regression with the help of software program SPSS for windows, version 16 (SPSS Inc., Somers, NY).

Fig-3: Bone marrow biopsy showing extensive metastatic deposit from small cell carcinoma of lung, having nests of small round cells with scanty cytoplasm and nuclear moldings (H & E X 100) and extensive myelofibrosis (H & E X 40).



Results

Our study group comprised of total 128 patients of bronchogenic carcinoma with male female ratio 3.92:1 and age varying from 35 to 78 years (mean age 57.6 ± 5.3 years). The major histological variety was squamous cell carcinoma (58 cases, 45.31%) followed by adenocarcinoma and small cell carcinoma (SCLC) as shown in table 1.

Table-1: Types of malignancy among study group

Type of malignancy	No. of patients (n=128)	Percentage of patients
Squamous cell carcinoma	58	45.31%
Adenocarcinoma	48	37.50%
Small cell carcinoma	22	17.18%
Total	128	100%

Majority of non small cell variety belonged to stage 3 and 4, whereas majority of small cell variety was in extensive stage (table 2). The commonest presenting feature was cough (78%), chest pain(53%) and shortness of breath (47%).

In our study group, bone marrow metastatic deposits were found in total 12 cases (9.37%) in both bone marrow trephine biopsy and aspirate. Among different histological varieties, small cell carcinoma has highest rate of marrow metastasis (6 cases, 27.27% of SCLC), followed by squamous cell (4 cases, 6.89% of squamous varietis) and adenocarcinoma (2 cases, 4.16% of adeno cases) (Table 3). (Figure 2,3) Notably, bone marrow aspiration was unable to detect metastasis in 2 cases (likely due to extensive myelofibrosis) where bone marrow trephine biopsy was useful. Both these missed cases belonged to small cell variety with grade 3 myelofibrosis. The grading of myelofibrosis by reticulin stain done. Interestingly majority of marrow metastatic group of patients belonged to grade 3 and 4 myelofibrosis (figure 4), whereas grade 2 and 1 was quite rare in such group.

Table-2: Pathological types and clinical stage of disease at the time of presentation

Type of malignancy	Stage of Patients	No. of patients	% age of total case
NSCLC	1 or 2	22	17.19%
	3	46	35.94%
	4	38	29.68%
SCLC	Limited disease	8	6.25%
	Extensive disease	14	10.94%
Total		128	100%

Table-3: Percentage of metastatic deposit observed in histological varieties in various procedures				
Types of malignancy	Metastatic deposit present			
	Aspiration		Biopsy	
	Number	Percentage	Number	Percentage
Squamous cell carcinoma	4	6.89%	4	6.89%
Adenocarcinoma	2	4.16%	2	4.16%
Small cell carcinoma	4	18.18%	6	27.27%
Total	10	7.81%	12	9.37%

Fig-4: Reticulin stain showing grade 3 reticulin fibrosis with coarse reticulin fibers (4A) and Grade 4 myelofibrosis (4B) in small cell carcinoma of lung in spite of free from metastatic deposit.

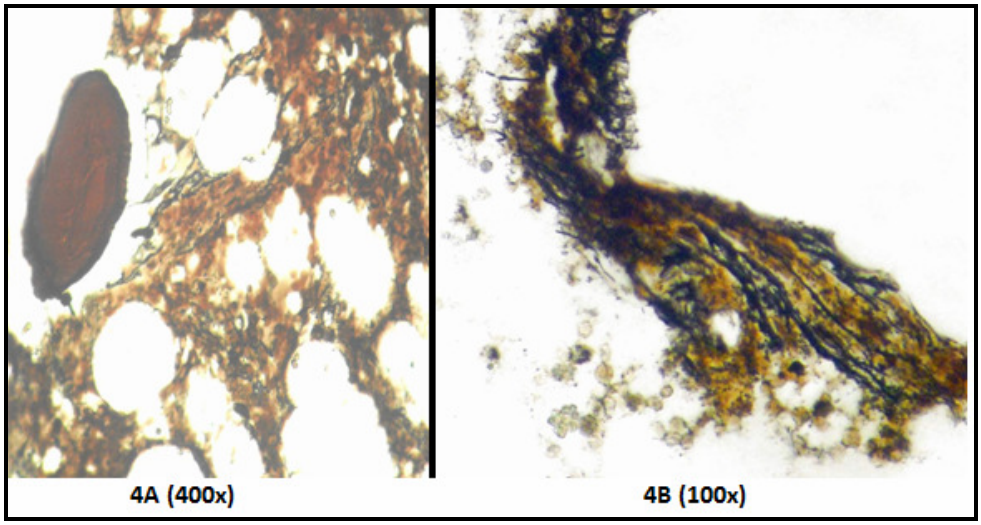


Table-4: Statistical significance of different hematological parameters and bone marrow metastasis						
Parameters	No marrow metastasis		With marrow metastasis		Two tailed P value	Interpretation of unpaired t test results
	Mean	Standard deviation	Mean	Standard deviation		
Hemoglobin	9.412	2.877	5.2	2.051	0.0023	Not statistically significant
Total WBC count	8710.345	3369.4	6483.33	4770	0.31096	Not statistically significant
Platelet count	1.0694	0.3958	0.385	0.1032	1.12766	Not statistically significant
LDH	618.965	440.277	1425	339.39	0.00110	Statistically significant
Uric acid	5.320	1.2460	7.433	0.4760	0.0001	Extremely Statistically significant
Alkaline phosphatase	354.137	164.295	730	342.870	0.04315	Not statistically significant
Calcium	9.8431	0.9281	11.91	1.710	0.0305	Not statistically significant

Analysis of hematological and biochemical parameters were done in cases with marrow metastasis and those without detectable metastatic deposit in bone marrow using unpaired t-test. We found statistically significant difference in LDH (p= 0.0011) and uric acid level (p= 0.0001) in two groups, but there was no significant correlation regarding other parameters (hemoglobin, leucocyte and platelet count, calcium and alkaline phosphatase level) (table 4). However, the patients with marrow metastasis showed pancytopenia with elevated levels of calcium, alkaline phosphatase, LDH and uric acid level compared to other group.

Discussion

Bone marrow is one of the most common organs involved by the tumors that metastasize by blood stream [3]. Hence it is imperative to rule out the bone marrow involvement in malignancies where treatment with curative intention is being considered. The early detection of bone marrow involvement at any phase of cancer evolution can significantly change the staging of the disease and thus alter the treatment stategy [8]. Even a small focus of metastatic tumor deposit will alter the tumor stage and according to TNM staging, evidence of distant metastasis indicate stage IV bronchogenic carcinoma rendering it inoperable where only supportive treatment is feasible.

Our study detected metastatic bone marrow deposit in total 12 cases (9.37%) of bronchogenic carcinoma. However, the relatively lower rate of metastasis detection (particularly in non small cell variety) compared to the global and Indian studies (table no. 5) can be attributed to the relatively earlier diagnosis of cases, exclusion of advanced stage cases i.e. patients already having metastatic spread to other site like metastatic lymph node deposit, positive pleural fluid cytology, hepatic,adrenal or cerebral metastasis.

Table-5: Percentage of bone marrow metastasis in different types of bronchogenic carcinoma in various studies

Name of the study	Small cell carcinoma	Non small cell carcinoma
Heine et al [13] 2006	46.4%	16.6%
Hansen et al [12] 1971	45% (9 out of 20)	4.08% (2 out of 49)
Dzieciol J et al [14] 1989	35.56% (16 out of 45)	28.81% (17 out of 59)
Broniek A et al [15] 1993	26.41% (28 out of 106)	Not studied
Lawrence JB et al [16] 1984	23.4% (30 out of 128)	Not studied
Hsu CP SL et al [17] 2000	Not studied	21.9% (21 out of 96)
Present Study	27.27% (6 out of 22)	5.66% (6 out of 106)

Infiltration of the bone marrow may be suspected on the basis of bone pain, pathological fractures, lytic lesions or sclerotic lesions demonstrated radiologically , unexplained 'hot spots' on isotopic bone scan, hypercalcaemia or elevated serum alkaline phosphatase activity and unexplained hematological abnormalities [5]. The hematological abnormality most suggestive of marrow infiltration, though not specific for it, is leuco-erythroblastic anemia [9].

We couldn't found such leucoerythroblastic picture in our cases, rather statistically significant correlation was observed only in LDH (p= 0.0011) and uric acid level (p= 0.0001). Another notable aspect is that usually marrow metastasis are associated with extensive marrow fibrosis, and thereby resulted in dry tap. The detection of tumor cells in a trephine biopsy when none are demonstrable in smears of an aspirate is not uncommon [10-11].

On the other hand, about three-quarters of metastases detected by trephine biopsy is detected by a simultaneous bone-marrow aspirate. Such a discrepancy between the

biopsy and aspirate findings is usually a result of a desmoplastic stromal reaction (fibrosis) to the tumor, which renders tumor cells more difficult to aspirate than residual hemopoietic cells. Therefore the two procedures should be regarded as complimentary. We have found extensive (grade 3 and 4) myelofibrosis in total 32 (25%) cases and 2 of such cases failed to show metastatic deposit in aspirate.

Conclusion

Henceforth we emphasized that the cytological and histological examination of bone marrow may be considered as one of the useful and safe pre-treatment staging procedures in bronchogenic carcinoma because early detection of sites of metastatic spread provides prognostic information that may be useful in the evaluation of alternative non-surgical treatment modalities.

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