

## Bone Marrow Involvement in Small Cell Lung Cancer

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### Abstract

Determination of bone marrow involvement is important in staging, treatment planning and the prognosis of SCLC. The aim of the present study is to find out the frequency of bone marrow involvement by bone marrow biopsy and its relation with the clinical and laboratory findings. For this reason, we have done bone marrow biopsy from the unilateral iliac bone crest of the 30 histopathologically diagnosed and therapy naive SCLC patients. We discovered bone marrow involvement in 9 patients (30%). While 8 of these cases had additional organ metastasis, in one of them bone marrow was the only metastatic focus. Haematologically, we detected leucoerythroblastosis in

the peripheral blood of 44% of the cases having bone marrow involvement and this was statistically significant with respect to the ones not having involvement ( $P < 0.01$ ). However, there wasn't a significant difference between the two groups by means of anaemia, thrombositopenia and other biochemical parameters. We also didn't establish any correlation between the bone marrow involvement and the bone scan.

*Turkish Respiratory Journal, 2004;5(1):32-35*

**Keywords:** immature testicular teratoma, endobronchial metastasis, pleural metastasis, mediastinal metastasis

### Introduction

SCLC forms 25% of the primary lung cancers and should be evaluated as a systemic disease because of its biologic behaviour. At the time of the initial diagnosis 80% of the cases have distant metastases (1), 10-15% have brain metastases, 28% have liver, 29% have bone and 17-30% have bone marrow metastases (2). In autopsy series, bone marrow involvement is about 40-50% (3,4). Performance status and the number of sites are important for the estimation of prognosis.

Aspiration, needle biopsy and imprint preparation from the biopsy are used for the determination of bone marrow metastases. But the most suitable way is the bone marrow biopsy examination. For the bone marrow needle biopsy procedure, generally iliac crest is used as it contains a wide marrow area and is easy and safe for application (5). For the peripheral smears papanicolau, for the block sections hematoxyline-eosine-staining techniques are used. During the last years monoclonal antibodies which are formed against SCLC tumour cells are investigated in the bone marrow with indirect immunoflouresance technique, which determines bone marrow metastases at a higher rate than the light microscopic examination. In a study which compared these two methods for 30 SCLC cases, a routine histopathologic examination that was performed at the same time determined only 6 (20%) bone marrow involvement cases while indirect immunoflouresance method determined 19 (63%) micro metastases (6).

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Invasion site	n	%
Liver	10	33.3
Bone marrow	9	30
Bone	8	26.6
Lenph node	6	20
Brain	5	16.6
Other	3	10

In our study, our aim was to determine the bone marrow involvement by bone marrow needle biopsy in SCLC and to determine the relationship with the clinical and laboratory findings of the bone marrow involvement.

## Materials and Methods

In our study, 30 chemotherapy and radiotherapy naive patients were evaluated who were diagnosed as SCLC in our center in 1995. For staging; detailed history, physical examination, lung roentgenography and routine biochemical techniques, thorax and brain tomography, abdomen ultrasonography, bone scintigraphy with technetium-99 and bone marrow biopsy were performed.

The performance status of the patients were evaluated with ECOG (Eastern Cooperative Oncology Group) staging(2).

The patients were staged in two different groups by the staging system, which was proposed for the inoperable tumours by VALC (Veterans Administration Lung Cancer) study group(7).

Bone marrow biopsy was done under sterile conditions from one iliac crest side by using 11 G4 Becton-Dickinson needle. The biopsy material was spread by touching lightly on to the slide, then put into the Holland solution for store. Spreaded materials was stained with papanicolau (E.A. 65) after fixation with 96% alcohol. Biopsy materials was washed in water for 5-6 hours after storing in Holland solution one night and stored in formic acid solution with 10% formalin the other night. The next day, the material was washed again in water and was treated as normal tissue preparation. The 3-4 thick sections, which were prepared in paraffin blocks were stained with hematoxylene eosin. These preparations were examined under light microscopy in the pathology laboratory of our center.

We evaluated the group which had bone marrow involvement as group I and the group which didn't have bone marrow involvement as group II. Group I had the same variance as the group II, numerical values were evaluated by using "independent samples T test" of the nonparametrical test. Fisher-exact- $\chi^2$  test and z-test were used for other statistical analysis.

## Results

Patients in this study were all men. Range 40-85, mean  $58.7 \pm 9.9$  years. There wasn't a history of exposure with a carcinogenic material in any of the patients. Ninety three per-

	Bone scintigraphy	
	(-)	(+)
Bone marrow spread (-)	17 (%56.6)	4 (%13.3)
Bone marrow spread (+)	5 (%16.6)	4 (%13.3)

cent of the patients were smoking more than 20 cigarettes per day and over 20 years.

Complaints in 80% of the patients was begun 6 month before the diagnosis. The most usual complaints were cough (n: 22, 73.3%), fatigue (n: 14, 46.6%), dyspnea (n: 11, 36%), sputum (n: 9, 30%) and pericordial pain (n: 9, 30%). Most of these initial complaints were due to primary tumour. 6 patients (75%) of the bone metastasis group (total no: 8), and 2 patients (22.2%) of the bone marrow involvement group (total no: 9) had bone pain. The difference between these two groups was found to be statistically significant ( $z=2.672$ ,  $p<0.01$ ). The most common findings in the physical examination were lymphadenomegaly (36.6%), jugular venous distention (16.6%), vocal cord paralysis (13.3%), hepatomegaly (10%), hypertension (10%) and vena cava superior syndrome (10%). Physical findings in three cases were found to be normal. The most common finding in the respiratory system examination was rale (n: 11, 36.6%).

The performance status of the patients according to WHO were evaluated as 2 (33.3%) for 10 cases, 1 (26.6%) for 8 cases, 3 (20%) for 6 cases and (10%) for 3 cases.

While bronchoscopy was used for diagnosis in 17 cases (56.6%), lymph node biopsy was performed in 7 cases (23.3%) and pleural biopsy in 2 cases (8.6%), the others were diagnosed by skin biopsy, sputum cytology and pleural fluid cytology.

Eight pats (26.6%) had limited, 22 cases (73.3%) had extensive stage disease.

Liver in 10 (33.3%) cases, bone marrow in 9 (30%) cases, bone in 8 (26.6%) cases, lymph node in 6 (20%) cases, brain in 5 (16.6%) cases, surrenal gland in 1 (3.33%) case, skin in 1 (3.33%) case and medullary canal in 1 (3.33%) case were invaded (Table 1).

In 13 (43.39%) patients bone scintigraphy and/or bone marrow involvement were positive. Five (16.7%) of the patients whose metastases couldn't be determined by scintigraphy had bone marrow involvement; 3 (10%) patients whose bone marrow involvement couldn't be determined had bone metastases. In 4 (13.3%) patients, both bone marrow biopsy and bone scintigraphy were positive (Table 2). Consequently, a relation wasn't found between bone marrow involvement and metastasis determination with bone scintigraphy ( $p<0.05$ ).

There wasn't statistically significant difference between group I and group II according to haemoglobin, leukocyte, platelet, erythrocyte, alkaline phosphatase, total protein, albumine, globuline, lactate dehydrogenase, sodium, potassium, phosphors and calcium values ( $p>0.05$ ) (Table 3).



Table 3. Comparing of the group of bone marrow invasion with the other, statistically

Parameter	Bone marrow invasion (+) Average±SD	Bone marrow invasion (-) Average±SD	P
Age	61.50±10.40	56.90±9.90	0.280
Hemoglobin (gr/dl)	12.20±1.12	12.37±1.34	0.734
Leucosit (mm <sup>3</sup> )	10.95±3.58	9.89±3.10	0.420
Trombosit (mm <sup>3</sup> )	243000±15818	315000±10576	0.149
Erythrocyte (x10000/(mm <sup>3</sup> ))	4.17±0.40	4.31±0.32	0.314
Alkalien Phosphatas (U/L)	90.44±28.27	85.61±25.67	0.650
Total protein (gr/dl)	6.87±0.49	7.12±0.64	0.309
Albumin (gr/dl)	3.32±0.36	3.46±0.49	0.451
LDH (U/L)	930±706	731±533	0.412
Sodium (mEq/L)	135.40±4.30	136.90±3.50	0.346
Potassium (mEq/L)	4.23±0.57	4.13±0.35	0.562
Phosphorus (mg/dl)	3.80±0.49	3.46±0.53	0.121
Calcium (mg/dl)	9.44±0.63	14.47±2.14	0.492

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Although group I, had leukoeritroblastosis in 4 cases, group II, hadn't leukoeritroblastosis in any case. The statistical difference between two groups was significant ( $p < 0.01$ ).

## Discussion

As for the small cell carcinoma of the lung, bone marrow is invaded in a 17-30% ratio, bone marrow needle biopsy is proposed for staging procedure. There are literatures, which propose that bone marrow aspiration is as sensitive as bone marrow biopsy for the determination of bone marrow involvement, however when the literatures are evaluated thoroughly, needle biopsy should be the choice (8,9,10). In our study, bone marrow needle biopsy was used. In none of the patients, there wasn't an important complaint according to this procedure. With light microscopic examination, 9 cases (30%) from the 30 patients had bone marrow involvement. This result was in accordance with literature. As it is known that bone marrow needle biopsy done from both iliac crests with taking multiple specimens doesn't increase the positive rate, we choose to make biopsy from one iliac crest (one side) and if necessary by taking more than one part.

Bone pain complaint, which is encountered commonly in bone metastasis, is encountered less commonly in bone marrow involvement (11). In our study when 7 cases who had bone pain complaint were evaluated, bone metastasis were found in 6 (n: 8, 75%) cases and bone marrow involvement in 1 (n: 9, 11%) case. Thus, we thought that bone marrow metastasis is commonly without pain and bone pain isn't a finding which suggests bone marrow metastasis.

There are a lot of literature suggesting that the laboratory findings aren't meaningful for bone marrow involvement (12,13), Also in our study, the groups didn't show significant differences according to haemoglobin, leukocyte values, platelet numbers and other biochemical tests ( $p > 0.05$ ).

In about 57% of the malignancies which invade bone marrow, leukoeritroblastosis is determined in the differential leukocyte count (14). Leukoeritroblastosis is undifferentiated cells of the myeloid and eritroid series in the peripheral blood and is always with extramedullar hematopoiesis. We didn't have any case that had leukoeritroblastosis in the peripheral leukocyte count, in group II. But, 4 leukoeritroblastosis cases was determined in group I. This was statistically significant ( $p < 0.01$ ).

For the determination of the bone metastases, bone scintigraphy is the most sensitive method for the malignant tumors (13). A correlation wasn't found between bone metastasis ratio determined with bone scintigraphy and bone marrow involvement ratio determined with bone marrow biopsy (1). In our study, 4 of 7 patients who had bone metastases had bone marrow involvement and 4 of 9 patients who had bone marrow involvement had bone metastases. With these results, we weren't able to find any correlation between bone marrow involvement and bone scintigraphy findings.

Determination of the bone marrow involvement rate by bone marrow needle biopsy in SCLC cases can be the only distant metastases finding of the disease in some cases (10). In our study, one case hadn't any metastases except bone marrow involvement. When the SCLC patient isn't suitable for the other invasive diagnose methods, bone marrow biopsy is

suggestive of the diagnose in a rate of about 67% (15). In addition to this, it is documented that bone marrow involvement was detected in most patients convencially staged as having limited disease (17).

There are some current studies about magnetic resonance imaging (MRI) of the bone medulla, however because of economic reason, we couldn't perform medullary magnetic resonance imaging. The studies performing MRI and unilateral iliac crest biopsy and sintigraphy together have yielded results in favour of the routine usage of MRI for SCLC staging (16).

In conclusion, for staging SCLC patients who are supposed to be in the local stage and for patients who had problems in histopathologic diagnosis, bone marrow needle biopsy can be proposed.

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